

Connecting via Winsock to Dialog

Logging in to Dialog

Trying 31060000009998...Open

DIALOG INFORMATION SERVICES

PLEASE LOGON:

ENTER PASSWORD:

Welcome to DIALOG

Dialog level 05.15.00D

Last logoff: 14dec06 16:06:16

Logon file405 18dec06 18:47:55

*** ANNOUNCEMENTS ***

NEW FILES RELEASED

***Engineering Index Backfile (File 988)

***Verdict Market Research (File 769)

***EMCare (File 45)

***Trademarkscan - South Korea (File 655)

RESUMED UPDATING

***File 141, Reader's Guide Abstracts

RELOADS COMPLETED

***Files 340, 341 & 942, CLAIMS/U.S. Patents - 2006 reload now online

***Files 173 & 973, Adis Clinical Trials Insight

***File 11, PsycInfo

***File 531, American Business Directory

DATABASES REMOVED

***File 196, FINDEX

***File 468, Public Opinion Online (POLL)

Chemical Structure Searching now available in Prous Science Drug

Data Report (F452), Prous Science Drugs of the Future (F453),

IMS R&D Focus (F445/955), Pharmaprojects (F128/928), Beilstein

Facts (F390), Derwent Chemistry Resource (F355) and Index Chemicus
(File 302).

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>>>and events, please visit What's New from Dialog at <<<

>>><http://www.dialog.com/whatsnew/>. You can find news about<<<

>>>a specific database by entering HELP NEWS <file number>. <<<

* * *

SYSTEM:HOME

Cost is in DialUnits

Menu System II: D2 version 1.8.0 term=ASCII

*** DIALOG HOMEBASE(SM) Main Menu ***

Information:

1. Announcements (new files, reloads, etc.)
2. Database, Rates, & Command Descriptions
3. Help in Choosing Databases for Your Topic
4. Customer Services (telephone assistance, training, seminars, etc.)
5. Product Descriptions

Connections:

6. DIALOG(R) Document Delivery
7. Data Star(R)

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/H = Help /L = Logoff /NOMENU = Command Mode

Enter an option number to view information or to connect to an online service. Enter a BEGIN command plus a file number to search a database (e.g., B1 for ERIC).

? b 410

```
18dec06 18:47:55 User228206 Session D2656.1
$0.00 0.240 DialUnits FileHomeBase
$0.00 Estimated cost FileHomeBase
$0.00 Estimated cost this search
$0.00 Estimated total session cost 0.240 DialUnits
```

File 410:Dialog Comm.-of-Interest News1/Jul (c) 2006 Dialog

Set Items Description

--- -----

? set hi ;set hi

HIGHLIGHT set on as ''

HIGHLIGHT set on as ''

? b 155

```
18dec06 18:47:58 User228206 Session D2656.2
$0.00 0.117 DialUnits File410
$0.00 Estimated cost File410
$0.00 Estimated cost this search
$0.00 Estimated total session cost 0.358 DialUnits
```

File 155: MEDLINE(R) 1950-2006/Dec 06

(c) format only 2006 Dialog

*File 155: MEDLINE has temporarily stopped updating with UD=20061206.
Please see HELP NEWS154 for details.

Set Items Description

--- -----

? e decubitis ulcers

Ref	Items	RT	Index-term
E1	1		DECUBITII
E2	14		DECUBITIS
E3	0		*DECUBITIS ULCERS
E4	2		DECUBITIUS
E5	128		DECUBITO
E6	1		DECUBITODEOXIA
E7	1		DECUBITORMADRASSEN
E8	2		DECUBITOS
E9	1		DECUBITOUS
E10	1		DECUBITUL
E11	3093		DECUBITUS
E12	122	1	DECUBITUS ULCER

Enter P or PAGE for more

? s e2 or e4

```
14 DECUBITIS
2 DECUBITIUS
S1 16 'DECUBITIS' OR 'DECUBITIUS'
```

? e bedsores

Ref	Items	RT	Index-term
E1	2		BEDSONIOZA
E2	41	1	BEDSORE
E3	241		*BEDSORES

E4	1	BEDSOSIAN
E5	6	BEDSPACE
E6	1	BEDSPACES
E7	1	BEDSPIRAAL
E8	2	BEDSPREAD
E9	2	BEDSPREADS
E10	1	BEDSPRINGS
E11	25	BEDST
E12	3	BEDSTAY

Enter P or PAGE for more

? s e2 or e3

	41	BEDSORE
	241	BEDSORES
S2	270	'BEDSORE' OR 'BEDSORES'

? e e2

Ref	Items	Type	RT	Index-term
R1	41		1	*BEDSORE
R2	6944	X	5	PRESSURE ULCER
? s r1:r2				
	S3	6949	R1:R2	
? e r2				

Ref	Items	Type	RT	Index-term
R1	6944		5	*PRESSURE ULCER
R2	6944	X		DC=C17.800.893.665. (PRESSURE ULCER)
R3	41	X	1	BEDSORE
R4	122	X	1	DECUBITUS ULCER
R5	0	X	1	PRESSURE SORE
R6	5266	B	7	SKIN ULCER
? s r1:r6				
	S4	12128	R1:R6	
? ds				

Set	Items	Description
S1	16	'DECUBITIS' OR 'DECUBITIUS'
S2	270	'BEDSORE' OR 'BEDSORES'
S3	6949	R1:R2
S4	12128	R1:R6
? s s1 or s2 or s3 or s4		
	16	S1
	270	S2
	6949	S3
	12128	S4
S5	12203	S1 OR S2 OR S3 OR S4

? e botulinum toxin

Ref	Items	RT	Index-term
E1	1		BOTULINUM NEUROTOXIN A (844-1250)
E2	1		BOTULINUM NEUROTOXIN A (870-1295)
E3	0		*BOTULINUM TOXIN
E4	2332	6	BOTULINUM TOXIN TYPE A
E5	852		BOTULINUM TOXIN TYPE A --ADMINISTRATION AND DO
E6	337		BOTULINUM TOXIN TYPE A --ADVERSE EFFECTS --AE
E7	22		BOTULINUM TOXIN TYPE A --ANALYSIS --AN
E8	41		BOTULINUM TOXIN TYPE A --ANTAGONISTS AND INHIB
E9	9		BOTULINUM TOXIN TYPE A --BIOSYNTHESIS --BI
E10	5		BOTULINUM TOXIN TYPE A --BLOOD --BL
E11	5		BOTULINUM TOXIN TYPE A --CHEMICAL SYNTHESIS --
E12	88		BOTULINUM TOXIN TYPE A --CHEMISTRY --CH

Enter P or PAGE for more

? s e4:e12

S6	2332	'BOTULINUM TOXIN TYPE A': 'BOTULINUM TOXIN TYPE A
----	------	---

--CHEMISTRY --CH'

? e e4

Ref	Items	Type	RT	Index-term
R1	2332		6	*BOTULINUM TOXIN TYPE A
R2	2332	X		DC=D12.776.97.156.50. (BOTULINUM TOXIN TYPE A)
R3	2332	X		DC=D23.946.123.179.50. (BOTULINUM TOXIN TYPE A)
R4	4710	B	13	BOTULINUM TOXINS
R5	1736	B	33	NEUROMUSCULAR AGENTS
R6	10157	B	15	NEUROTOXINS
R7	293	B	232	NOXAE
? s sr:r4				
	S7		0	SR:'BOTULINUM TOXINS'
? s r1:r4				
	S8		6862	R1:R4
? ds				

Set	Items	Description
S1	16	'DECUBITIS' OR 'DECUBITIUS'
S2	270	'BEDSORE' OR 'BEDSORES'
S3	6949	R1:R2
S4	12128	R1:R6
S5	12203	S1 OR S2 OR S3 OR S4
S6	2332	'BOTULINUM TOXIN TYPE A': 'BOTULINUM TOXIN TYPE A --CHEMIST- RY --CH'
S7	0	SR:'BOTULINUM TOXINS'
S8	6862	R1:R4
? s botulinum?		
	S9	9613 BOTULINUM?
? s botox		
	S10	607 BOTOX
? s dysport		
	S11	181 DYSSPORT
? s myoblc		
	S12	0 MYOBLIC
? s myobloc		
	S13	45 MYOBLOC
? ds		

Set	Items	Description
S1	16	'DECUBITIS' OR 'DECUBITIUS'
S2	270	'BEDSORE' OR 'BEDSORES'
S3	6949	R1:R2
S4	12128	R1:R6
S5	12203	S1 OR S2 OR S3 OR S4
S6	2332	'BOTULINUM TOXIN TYPE A': 'BOTULINUM TOXIN TYPE A --CHEMIST- RY --CH'
S7	0	SR:'BOTULINUM TOXINS'
S8	6862	R1:R4
S9	9613	BOTULINUM?
S10	607	BOTOX
S11	181	DYSSPORT
S12	0	MYOBLIC
S13	45	MYOBLOC
? s s5 and (s6 or s8 or s9 or s10 or s11 or s13)		
	12203	S5
	2332	S6
	6862	S8
	9613	S9
	607	S10
	181	S11
	45	S13
S14	0	S5 AND (S6 OR S8 OR S9 OR S10 OR S11 OR S13)
? s s6 or s8 or s9 or s10 or s11 or s13		
	2332	S6

```

6862 S8
9613 S9
607 S10
181 S11
45 S13
S15 9642 S6 OR S8 OR S9 OR S10 OR S11 OR S13
? s pressur? (3n) sore?
659992 PRESSUR?
9071 SORE?
S16 1981 PRESSUR? (3N) SORE?
? ds

```

Set	Items	Description
S1	16	'DECUBITIS' OR 'DECUBITIUS'
S2	270	'BEDSORE' OR 'BEDSORES'
S3	6949	R1:R2
S4	12128	R1:R6
S5	12203	S1 OR S2 OR S3 OR S4
S6	2332	'BOTULINUM TOXIN TYPE A': 'BOTULINUM TOXIN TYPE A --CHEMIST- RY --CH'
S7	0	SR: 'BOTULINUM TOXINS'
S8	6862	R1:R4
S9	9613	BOTULINUM?
S10	607	BOTOX
S11	181	DYSPORT
S12	0	MYOBLC
S13	45	MYOBLOC
S14	0	S5 AND (S6 OR S8 OR S9 OR S10 OR S11 OR S13)
S15	9642	S6 OR S8 OR S9 OR S10 OR S11 OR S13
S16	1981	PRESSUR? (3N) SORE?
? s s15 and s16		
	9642	S15
	1981	S16
S17	1	S15 AND S16
? t s17/9/all		

17/9/1
DIALOG(R) File 155: MEDLINE(R)
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14600447 PMID: 14636486
Treatments for spasticity and pain in multiple sclerosis: a systematic review.
Beard S; Hunn A; Wight J
School of Health and Related Research (ScHARR), University of Sheffield, UK.
Health technology assessment (Winchester, England) (England) 2003, 7
(40) piii, ix-x, 1-111, ISSN 1366-5278--Print Journal Code: 9706284
Publishing Model Print
Document type: Journal Article; Review
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Subfile: INDEX MEDICUS
OBJECTIVES: To identify the drug treatments currently available for the management of spasticity and pain in multiple sclerosis (MS), and to evaluate their clinical and cost-effectiveness. DATA SOURCES: Electronic bibliographic databases, National Research Register, MRC Clinical Trials Register and the US National Institutes of Health Clinical Trials Register.
REVIEW METHODS: Systematic searches identified 15 interventions for the treatment of spasticity and 15 interventions for treatment of pain. The quality and outcomes of the studies were evaluated. Reviews of the treatment of spasticity and pain when due to other aetiologies were also sought. RESULTS: There is limited evidence of the effectiveness of four oral drugs for spasticity: baclofen, dantrolene, diazepam and tizanidine.

Tizanidine appears to be no more effective than comparator drugs such as baclofen and has a slightly different side-effects profile. Despite claims that it causes less muscle weakness, there was very little evidence that tizanidine performed any better in this respect than other drugs, although it is more expensive. The findings of this review are consistent with reviews of the same treatments for spasticity derived from other aetiologies. There is good evidence that both botulinum toxin (BT) and intrathecal baclofen are effective in reducing spasticity, and both are associated with functional benefit. However, they are invasive, and substantially more expensive. None of the studies included in the review of pain were designed specifically to evaluate the alleviation of pain in patients with MS and there was no consistency regarding the use of validated outcome measures. It was suggested that, although expensive, the use of intrathecal baclofen may be associated with significant savings in hospitalisation costs in relation to bed-bound patients who are at risk of developing pressure sores, thus enhancing its cost-effectiveness. No studies of cost-effectiveness were identified in the review of pain. There is evidence, albeit limited, of the clinical effectiveness of baclofen, dantrolene, diazepam, tizanidine, intrathecal baclofen and BT and of the potential cost-effectiveness of intrathecal baclofen in the treatment of spasticity in MS.

CONCLUSIONS: Many of the interventions identified are not licensed for the alleviation of pain or spasticity in MS and the lack of evidence relating to their effectiveness may also limit their widespread use. Indeed, forthcoming information relating to the use of cannabinoids in MS may result in there being better evidence of the effectiveness of new treatments than of any of the currently used drugs. It may therefore be of value to carry out double-blind randomised controlled trials of interventions used in current practice, where outcomes could include functional benefit and impact on quality of life. Further research into the development and validation of outcomes measures for pain and spasticity may also be useful, as perhaps would cost-utility studies. (154 Refs.)

Descriptors: *Multiple Sclerosis--physiopathology--PP; *Muscle Spasticity --drug therapy--DT; *Pain--drug therapy--DT; Adolescent; Adult; Clinical Trials; Comparative Study; Cost-Benefit Analysis; Evidence-Based Medicine; Great Britain; Humans; Middle Aged; Multiple Sclerosis--complications--CO; Muscle Relaxants, Central--therapeutic use--TU; Muscle Spasticity--etiology --ET; Pain--etiology--ET; Treatment Outcome

CAS Registry No.: 0 (Muscle Relaxants, Central)

Record Date Created: 20031125

Record Date Completed: 20040304

? ds

Set	Items	Description
S1	16	'DECUBITIS' OR 'DECUBITIUS'
S2	270	'BEDSORE' OR 'BEDSORES'
S3	6949	R1:R2
S4	12128	R1:R6
S5	12203	S1 OR S2 OR S3 OR S4
S6	2332	'BOTULINUM TOXIN TYPE A': 'BOTULINUM TOXIN TYPE A --CHEMIST- RY --CH'
S7	0	SR: 'BOTULINUM TOXINS'
S8	6862	R1:R4
S9	9613	BOTULINUM?
S10	607	BOTOX
S11	181	DYSPOINT
S12	0	MYOBLIC
S13	45	MYOBLOC
S14	0	S5 AND (S6 OR S8 OR S9 OR S10 OR S11 OR S13)
S15	9642	S6 OR S8 OR S9 OR S10 OR S11 OR S13
S16	1981	PRESSUR? (3N) SORE?
S17	1	S15 AND S16
? s s5 and wheel?		
	12203	S5
	8379	WHEEL?

S18 214 S5 AND WHEEL?
? s s18 and chair?
214 S18
9520 CHAIR?
S19 20 S18 AND CHAIR?
? t s19/9/all

19/9/1
DIALOG(R) File 155: MEDLINE(R)
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20667322 PMID: 16594122
The chair: low-tech device helps prevent pressure ulcers.
Olshansky Kenneth
Advances in skin & wound care (United States) Mar 2006, 19 (2) p68,
ISSN 1527-7941--Print Journal Code: 100911021
Publishing Model Print
Document type: Letter
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Subfile: NURSING
Descriptors: *Interior Design and Furnishings; *Posture; *Pressure
Ulcer--prevention and control--PC; *Wheelchairs; Bed Rest--adverse
effects--AE; Humans; Pressure Ulcer--etiology--ET
Record Date Created: 20060404
Record Date Completed: 20060505

19/9/2
DIALOG(R) File 155: MEDLINE(R)
(c) format only 2006 Dialog. All rts. reserv.

20538236 PMID: 16566743
Scientific basis for the selection of absorbent underpads that remain
securely attached to underlying bed or chair.
Edlich Richard F; Winters Kathryn L; Long William B; Gubler K Dean
University of Virginia Health System, Charlottesville, USA.
richardedlichmd@gmail.com
Journal of long-term effects of medical implants (United States) 2006;
16 (1) p29-40, ISSN 1050-6934--Print Journal Code: 9110830
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Subfile: HEALTH TECHNOLOGY ASSESSMENT
The occurrence of pressure ulcers in patients is very high in certain
high-risk groups. These special high-risk groups include elderly patients,
patients with spinal cord injuries, or any individual with an impaired
ability to reposition. Prevention of pressure ulcers is by far the best
treatment of this condition, warranting certain interventions and
preventive measures. One major risk factor to be minimized is the exposure
of skin to moisture. Underpads are often used to protect the skin of
patients who are incontinent. These products effectively absorb moisture
and present a quick-drying surface to the skin. The construction of an
underpad should accomplish three goals. First, its backing should have a
low coefficient of friction to prevent frictional skin injuries. Second, an
inner absorbent core should rapidly contain moisture and disseminate it
throughout the entire pad. Third, the core and coverstock should
successfully work together to retain moisture and prevent wet-back or fluid
return. The purpose of this study was to determine the performance of three
commercially available underpads in reducing the development of pressure
sores in patients at high risk. In

Set	Items	Description
S1	16	'DECUBITIS' OR 'DECUBITIUS'
S2	270	'BEDSORE' OR 'BEDSORES'
S3	6949	R1:R2
S4	12128	R1:R6
S5	12203	S1 OR S2 OR S3 OR S4
S6	2332	'BOTULINUM TOXIN TYPE A': 'BOTULINUM TOXIN TYPE A --CHEMIST-- RY --CH'
S7	0	SR: 'BOTULINUM TOXINS'
S8	6862	R1:R4
S9	9613	BOTULINUM?
S10	607	BOTOX
S11	181	DYSPORT
S12	0	MYOBLIC
S13	45	MYOBLOC
S14	0	S5 AND (S6 OR S8 OR S9 OR S10 OR S11 OR S13)
S15	9642	S6 OR S8 OR S9 OR S10 OR S11 OR S13
S16	1981	PRESSUR? (3N) SORE?
S17	1	S15 AND S16
S18	214	S5 AND WHEEL?
S19	20	S18 AND CHAIR? ? s s19 and (s6 or s8 or s9 or s10 or s11 or s12 or s13 or bontoxilysin? or bonta? or bota?)
	20	S19
	2332	S6
	6862	S8
	9613	S9
	607	S10
	181	S11
	0	S12
	45	S13
	0	BONTOXILYSIN?
	43	BONTA?
	3557	BOTA?
S20	0	S19 AND (S6 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR BONTOXILYSIN? OR BONTA? OR BOTA?)

?

14600447 PMID: 14636486

Treatments for spasticity and pain in multiple sclerosis: a systematic review.

Beard S; Hunn A; Wight J

School of Health and Related Research (ScHARR), University of Sheffield, UK.

Health technology assessment (Winchester, England) (England) 2003, 7

(40) piii, ix-x, 1-111, ISSN 1366-5278--Print Journal Code: 9706284

Publishing Model Print

Document type: Journal Article; Review

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

Subfile: INDEX MEDICUS

OBJECTIVES: To identify the drug treatments currently available for the management of spasticity and pain in multiple sclerosis (MS), and to evaluate their clinical and cost-effectiveness. **DATA SOURCES:** Electronic bibliographic databases, National Research Register, MRC Clinical Trials Register and the US National Institutes of Health Clinical Trials Register. **REVIEW METHODS:** Systematic searches identified 15 interventions for the treatment of spasticity and 15 interventions for treatment of pain. The quality and outcomes of the studies were evaluated. Reviews of the treatment of spasticity and pain when due to other aetiologies were also sought. **RESULTS:** There is limited evidence of the effectiveness of four oral drugs for spasticity: baclofen, dantrolene, diazepam and tizanidine. Tizanidine appears to be no more effective than comparator drugs such as baclofen and has a slightly different side-effects profile. Despite claims that it causes less muscle weakness, there was very little evidence that tizanidine performed any better in this respect than other drugs, although it is more expensive. The findings of this review are consistent with reviews of the same treatments for spasticity derived from other aetiologies. There is good evidence that both ***botulinum*** toxin (BT) and intrathecal baclofen are effective in reducing spasticity, and both are associated with functional benefit. However, they are invasive, and substantially more expensive. None of the studies included in the review of pain were designed specifically to evaluate the alleviation of pain in patients with MS and there was no consistency regarding the use of validated outcome measures. It was suggested that, although expensive, the use of intrathecal baclofen may be associated with significant savings in hospitalisation costs in relation to bed-bound patients who are at risk of developing pressure sores, thus enhancing its cost-effectiveness. No studies of cost-effectiveness were identified in the review of pain. There is evidence, albeit limited, of the clinical effectiveness of baclofen, dantrolene, diazepam, tizanidine, intrathecal baclofen and BT and of the potential cost-effectiveness of intrathecal baclofen in the treatment of spasticity in MS. **CONCLUSIONS:** Many of the interventions identified are not licensed for the alleviation of pain or spasticity in MS and the lack of evidence relating to their effectiveness may also limit their widespread use. Indeed, forthcoming information relating to the use of cannabinoids in MS may result in there being better evidence of the effectiveness of new treatments than of any of the currently used drugs. It may therefore be of value to carry out double-blind randomised controlled trials of interventions used in current practice, where outcomes could include functional benefit and impact on quality of life. Further research into the development and validation of outcomes measures for pain and spasticity may also be useful, as perhaps would cost-utility studies. (154 Refs.)

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CAS Registry No.: 0 (Muscle Relaxants, Central)

Record Date Created: 20031125

Record Date Completed: 20040304

?

5/9/1 (Item 1 from file: 155)

DIALOG(R) File 155: MEDLINE(R)

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14600447 PMID: 14636486

Treatments for spasticity and pain in multiple sclerosis: a systematic review.

Beard S; Hunn A; Wight J

School of Health and Related Research (SCHARR), University of Sheffield, UK.

Health technology assessment (Winchester, England) (England) 2003, 7 (40) piii, ix-x, 1-111, ISSN 1366-5278--Print Journal Code: 9706284 Publishing Model Print

Document type: Journal Article; Review

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

Subfile: INDEX MEDICUS

OBJECTIVES: To identify the drug treatments currently available for the management of spasticity and pain in multiple sclerosis (MS), and to evaluate their clinical and cost-effectiveness. **DATA SOURCES:** Electronic bibliographic databases, National Research Register, MRC Clinical Trials Register and the US National Institutes of Health Clinical Trials Register.

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Descriptors: *Multiple Sclerosis--physiopathology--PP; *Muscle Spasticity --drug therapy--DT; *Pain--drug therapy--DT; Adolescent; Adult; Clinical Trials; Comparative Study; Cost-Benefit Analysis; Evidence-Based Medicine;

Great Britain; Humans; Middle Aged; Multiple Sclerosis--complications--CO;
Muscle Relaxants, Central--therapeutic use--TU; Muscle Spasticity--etiology
--ET; Pain--etiology--ET; Treatment Outcome
CAS Registry No.: 0 (Muscle Relaxants, Central)
Record Date Created: 20031125
Record Date Completed: 20040304

5/9/2 (Item 2 from file: 155)
DIALOG(R) File 155: MEDLINE(R)
(c) format only 2006 Dialog. All rts. reserv.

13984041 PMID: 12388760
Tenascin-C modulates matrix contraction via focal adhesion kinase- and Rho-mediated signaling pathways.

Midwood Kim S; Schwarzauer Jean E
Department of Molecular Biology, Princeton University, Princeton, New Jersey 08544-1014, USA.

Molecular biology of the cell (United States) Oct 2002, 13 (10)
p3601-13, ISSN 1059-1524--Print Journal Code: 9201390

Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Subfile: INDEX MEDICUS; Toxbib

A provisional matrix consisting of fibrin and fibronectin (FN) is deposited at sites of tissue damage and repair. This matrix serves as a scaffold for fibroblast migration into the wound where these cells deposit new matrix to replace lost or damaged tissue and eventually contract the matrix to bring the margins of the wound together. Tenascin-C is expressed transiently during wound repair in tissue adjacent to areas of injury and contacts the provisional matrix *in vivo*. Using a synthetic model of the provisional matrix, we have found that tenascin-C regulates cell responses to a fibrin-FN matrix through modulation of focal adhesion kinase (FAK) and RhoA activation. Cells on fibrin-FN+tenascin-C redistribute their actin to the cell cortex, downregulate focal adhesion formation, and do not assemble a FN matrix. Cells surrounded by a fibrin-FN+tenascin-C matrix are unable to induce matrix contraction. The inhibitory effect of tenascin-C is circumvented by downstream activation of RhoA. FAK is also required for matrix contraction and the absence of FAK cannot be overcome by activation of RhoA. These observations show dual requirements for both FAK and RhoA activities during contraction of a fibrin-FN matrix. The effects of tenascin-C combined with its location around the wound bed suggest that this protein regulates fundamental processes of tissue repair by limiting the extent of matrix deposition and contraction to fibrin-FN-rich matrix in the primary wound area.

Descriptors: *Extracellular Matrix--metabolism--ME; *Protein-Tyrosine Kinase--metabolism--ME; *Signal Transduction--physiology--PH; *Tenascin --metabolism--ME; *rhoA GTP-Binding Protein--metabolism--ME; 3T3 Cells; ADP Ribose Transferases--pharmacology--PD; Amides--pharmacology--PD; Animals; Botulinum Toxins--pharmacology--PD; Cytoskeletal Proteins--metabolism --ME; Enzyme Inhibitors--pharmacology--PD; Fibrin--metabolism--ME; Fibroblasts--cytology--CY; Fibroblasts--drug effects--DE; Fibroblasts --metabolism--ME; Fibronectins--metabolism--ME; Focal Adhesion Kinase 1; Focal Adhesion Protein-Tyrosine Kinases; Focal Adhesions--metabolism--ME; Humans; Mice; Microscopy, Fluorescence; Phosphorylation; Protein-Tyrosine Kinase--genetics--GE; Pyridines--pharmacology--PD; Rats; Recombinant Proteins--metabolism--ME; Research Support, U.S. Gov't, P.H.S.; Simvastatin --pharmacology--PD; Stress Fibers--metabolism--ME; Vinculin--metabolism--ME ; Wound Healing--physiology--PH

CAS Registry No.: 0 (Amides); 0 (Botulinum Toxins); 0 (Cytoskeletal Proteins); 0 (Enzyme Inhibitors); 0 (Fibronectins); 0 (Pyridines); 0 (Recombinant Proteins); 0 (Tenascin); 125361-02-6 (Vinculin);

138381-45-0 (Y 27632); 79902-63-9 (Simvastatin); 9001-31-4 (Fibrin)
Enzyme No.: EC 2.4.2.- (ADP Ribose Transferases); EC 2.4.2.-
(exoenzyme C3, Clostridium ***botulinum***); EC 2.7.1.112 (Focal Adhesion
Kinase 1); EC 2.7.1.112 (Focal Adhesion Protein-Tyrosine Kinases); EC
2.7.1.112 (PTK2 protein, human); EC 2.7.1.112 (Protein-Tyrosine Kinase)
; EC 2.7.1.112 (Ptk2 protein, mouse); EC 2.7.1.112 (Ptk2 protein, rat);
EC 3.6.5.2 (rhoA GTP-Binding Protein)
Record Date Created: 20021025
Record Date Completed: 20030702

5/9/3 (Item 3 from file: 155)
DIALOG(R) File 155: MEDLINE(R)
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13823437 PMID: 12105839
Long-term follow-up (42 months) of chronic anal fissure after healing
with ***botulinum*** toxin.

Minguez Miguel; Herreros Belen; Espi Alejandro; Garcia-Granero Eduardo;
Sanchiz Vicente; Mora Francisco; Lledo Salvador; Benages Adolfo

Department of Gastroenterology, Clinic Hospital, University of Valencia,
Valencia, Spain. mminguezp@meditex.es

Gastroenterology (United States) Jul 2002, 123 (1) p112-7, ISSN
0016-5085--Print Journal Code: 0374630

Publishing Model Print; Comment in Gastroenterology. 2003 Apr;124(4) 1165
; Comment in PMID 12671920

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

Subfile: AIM; INDEX MEDICUS; Toxbib

BACKGROUND & AIMS: Botulinum toxin is an effective treatment in idiopathic chronic anal fissure, but the long-term outcome after healing is not well documented. We analyzed the long-term outcome of patients in whom an anal fissure had healed after botulinum toxin injection and the factors contributing to recurrence. METHODS: Fifty-seven patients who had completely healed 6 months after injection of botulinum toxin were reassessed every 6 months. The follow-up was 42 months in all patients. Clinical and manometric differences between the permanently healed and the relapsed group were statistically analyzed. RESULTS: Four patients were lost to follow-up. A fissure recurrence was shown in 22 patients (41.5%). Statistical differences between the permanently healed and the relapsed group were detected when analyzing the anterior location of the fissure (6% vs. 45%), a longer duration of the disease (38% vs. 68%), the need for reinjection (26% vs. 59%), a higher total dose injected to achieve definitive healing (13% vs. 45%), and the percentage decrease of maximum squeeze pressure after injection (-28% vs. -13%; P < 0.05). CONCLUSIONS: The late recurrence rate of chronic anal fissure is high when the effect of ***botulinum*** toxin disappears. The highest risk of recurrence is associated with anterior location of the anal fissure, prolonged illness, the need for reinjection and for high doses to achieve healing, and a lower decrease of maximum squeeze pressure after treatment.

Tags: Female; Male

Descriptors: *Botulinum Toxins--therapeutic use--TU; *Fissure in Ano--drug therapy--DT; Adult; Aged; Botulinum Toxins--administration and dosage--AD; Chronic Disease; Dose-Response Relationship, Drug; Fissure in Ano--physiopathology--PP; Follow-Up Studies; Humans; Injections; Middle Aged; Pressure; Recurrence; Retreatment; Wound Healing--drug effects--DE

CAS Registry No.: 0 (Botulinum Toxins)

Record Date Created: 20020709

Record Date Completed: 20020816

5/9/4 (Item 4 from file: 155)
DIALOG(R) File 155: MEDLINE(R)
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10963374 PMID: 8772071

The management of chronic fissure in-ano with ***botulinum*** toxin.
Mason P F; Watkins M J; Hall H S; Hall A W
Department of Surgery, Glenfield General Hospital, Leicester, UK.
Journal of the Royal College of Surgeons of Edinburgh (ENGLAND) Aug
1996, 41 (4) p235-8, ISSN 0035-8835--Print Journal Code: 7503110
Publishing Model Print; Comment in J R Coll Surg Edinb. 1997
Aug;42(4):288-9; Comment in PMID 9276578; Comment in J R Coll Surg Edinb.
1997 Aug;42(4):289; Comment in PMID 9276579; Comment in J R Coll Surg
Edinb. 1997 Aug;42(4):289-90; Comment in PMID 9276580

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

Subfile: INDEX MEDICUS; Toxbib

Five patients with a chronic fissure in-ano each received an injection of Clostridium botulinum type A toxin into the lower internal anal sphincter. A mean lowering of maximum resting anal pressure by 23.3 (SEM 5.6) cm H₂O was achieved within seven days. Maximum voluntary squeeze pressures were not significantly altered. Anal compliance increased in all cases. Healing of the fissure with an apparent reduction in anal sensation occurred in three of the patients and partial resolution of symptoms in the other two. No adverse effects resulted from injections of the toxin. A controlled trial to compare the relative efficacies of botulinum toxin and lateral sphincterotomy is required.

Tags: Male

Descriptors: *Botulinum Toxins--therapeutic use--TU; *Cholinergic Antagonists--therapeutic use--TU; *Fissure in Ano--therapy--TH; Adult; Aged; Anal Canal--drug effects--DE; Anal Canal--physiopathology--PP; Anal Canal--radiography--RA; Barium Sulfate--diagnostic use--DU; Botulinum Toxins--administration and dosage--AD; Cholinergic Antagonists--administration and dosage--AD; Chronic Disease; Comparative Study; Contrast Media; Controlled Clinical Trials; Defecation; Electromyography; Enema; Fissure in Ano--physiopathology--PP; Fissure in Ano--radiography--RA; Fissure in Ano--surgery--SU; Humans; Injections; Middle Aged; Muscle Contraction--drug effects--DE; Pressure; Sensation; Wound

Healing

CAS Registry No.: 0 (Botulinum Toxins); 0 (Cholinergic Antagonists); 0 (Contrast Media); 7727-43-7 (Barium Sulfate)

Record Date Created: 19961024

Record Date Completed: 19961024

5/9/5 (Item 1 from file: 34)
DIALOG(R) File 34: SciSearch(R) Cited Ref Sci
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08338374 Genuine Article#: 272YD Number of References: 38

Title: Rehabilitation after traumatic brain injury

Author(s): Barnes MP (REPRINT)

Corporate Source: UNIV NEWCASTLE UPON TYNE, HUNTERS MOOR REG NEUROREHABIL CTR, ACAD UNIT NEUROL REHABIL, HUNTERS RD/NEWCASTLE UPON TYNE NE2 4NR/TYNE & WEAR/ENGLAND/ (REPRINT)

Journal: BRITISH MEDICAL BULLETIN, 1999, V55, N4, P927-943

ISSN: 0007-1420 Publication date: 19990000

Publisher: ROYAL SOC MEDICINE PRESS LTD, 1 WIMPOLE STREET, LONDON W1M 8AE, ENGLAND

Language: English Document Type: ARTICLE

Geographic Location: ENGLAND

Subfile: CC LIFE--Current Contents, Life Sciences; CC CLIN--Current

Contents, Clinical Medicine;

Journal Subject Category: MEDICINE, GENERAL & INTERNAL

Abstract: Head injury is a common disabling condition but regrettably facilities for rehabilitation are sparse. There is now increasing evidence of the efficacy of a comprehensive multidisciplinary rehabilitation team compared to natural recovery following brain injury. This chapter outlines some basic concepts of rehabilitation and emphasises the importance of valid and reliable outcome measures. The evidence of the efficacy of a rehabilitation programme is discussed in some detail. A number of specific rehabilitation problems are outlined including the management of spasticity, nutrition, pressure

sores and urinary continence. The increasingly important role of assistive technology is illustrated, particularly in terms of communication aids and environmental control equipment. However, the major long-term difficulties after head injury focus around the cognitive, intellectual, behavioural and emotional problems. The complex management of these disorders is briefly addressed and the evidence of the efficacy of some techniques discussed. The importance of recognition of the vegetative state and avoidance of misdiagnosis is emphasised. Finally, the important, but often neglected, area of employment rehabilitation is covered.

Identifiers--KeyWord Plus(R): UPPER EXTREMITY SPASTICITY; SEVERE HEAD-INJURY; EARLY INTERVENTION; CONTROLLED TRIAL; BOTULINUM TOXIN; FOLLOW-UP; RELATIVES; EFFICACY

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5/9/6 (Item 2 from file: 34)
DIALOG(R) File 34:SciSearch(R) Cited Ref Sci
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07692747 Genuine Article#: 197GQ Number of References: 41
Title: Intrathecal baclofen therapy for spasticity of cerebral origin:

Cerebral palsy and brain injury

Author(s): Nuttin B (REPRINT) ; Ivanhoe C; Albright L; Dimitrijevic M;
Saltuari L

Corporate Source: UZ GASTHUISBERG,DEPT NEUROSURG, HERESTRAAT 49/B-3000
LOUVAIN//BELGIUM/ (REPRINT); INST REHABIL & RES,/HOUSTON//TX/; UNIV
PITTSBURGH,CHILDRENS HOSP, SCH MED/PITTSBURGH//PA/; BAYLOR COLL
MED,DEPT PHYS MED & REHABIL/HOUSTON//TX/; DEPT NEUROL
REHABIL,/ZIRL//AUSTRIA/

Journal: NEUROMODULATION; 1999, V2, N2 (APR), P120-132

ISSN: 1094-7159 Publication date: 19990400

Publisher: BLACKWELL SCIENCE INC, 350 MAIN ST, MALDEN, MA 02148

Language: English Document Type: ARTICLE

Geographic Location: BELGIUM; USA; AUSTRIA

Journal Subject Category: CLINICAL NEUROLOGY; MEDICINE, RESEARCH &
EXPERIMENTAL

Abstract: Spasticity affects approximately 66% of individuals with cerebral palsy and 14% of the 100,000 individuals who, each year, experience brain injury in the US. This spasticity interferes with motor function and limits range of motion. It may cause pain and impede mobility, transfers, activities of daily living, sitting posture, and sleep. In addition, spasticity can contribute to the formation of pressure sores and joint contractures and make nursing or caregiving difficult. Several treatment options are available for intractable spasticity. For some diagnoses, oral medications are still the treatment of choice, while in other settings injection therapy may be more appropriate. If, however, they are ineffective or cause too many side effects, intrathecal baclofen therapy (ITB) may be a valuable alternative. ITB is effective, nondestructive, titratable, and reversible; in addition, it is associated with fewer CNS-related side effects than oral Lioresal (Novartis Pharma AG, Basel, Switzerland). Intrathecal baclofen therapy may improve range of motion, facilitate movement, reduce the patient's expenditure of energy, facilitate nursing, reduce the risk of developing contractures; and, in some cases, diminish pain resulting from spasticity and/or spasms; It also may improve speech, gait, upper extremity function, and activities of daily living, including communication, eating, dressing, hygiene, and other aspects of self-care. A recent study shows that treatment with intrathecal baclofen reduces the need for corrective orthopedic surgeries. Patient selection should be done in a multidisciplinary spasticity setting, where the expertise for different treatment modalities is available; Patients must be screened for response to the drug prior to implantation of the drug delivery pump. Maintenance doses for intrathecal baclofen range from 22 to 1400 mu g/day, with most patients adequately maintained on 90-703 mu g/day. Complications, while rare, are most often related to the drug delivery catheter. Intrathecal baclofen treatment maybe-cost effective, primarily due to a reduced need for hospitalizations and treatment of adverse events related to uncontrolled spasticity, and may improve quality of life;

Intrathecal baclofen shows long-term efficacy in both higher and lower level patients with cerebral origin spasticity.

Descriptors--Author Keywords: baclofen ; brain injury ; cerebral palsy ; drug therapy ; intrathecal infusion ; stroke

Identifiers--KeyWord Plus(R): BOTULINUM TOXIN; SPINAL ORIGIN;
DRUG-THERAPY; INFUSION; CHILDREN

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5/9/7 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE
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11839610 EMBASE No: 2002412801
Treatment of resistant anal fissure with advancement anoplasty
Kenefick N.J.; Gee A.S.; Durdey P.
N.J. Kenefick, St. Mark's Hospital, Watford Road, Harrow, Middlesex HA1
3UJ United Kingdom
AUTHOR EMAIL: nickkenefick@hotmail.com
Colorectal Disease (COLORECTAL DIS.) (United Kingdom) 2002, 4/6
(463-466)
CODEN: CODIF ISSN: 1462-8910
DOCUMENT TYPE: Journal ; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 19

Objective. The primary aim of this study was to assess the outcome of advancement anoplasty in the treatment of chronic anal fissure, resistant to conventional therapy. The secondary aim was to evaluate the anal resting pressure in these patients with resistant fissures. Patients and methods. Over a five-year period eight patients (2 male, median age 55 years, range

20-74) with resistant anal fissure were referred from 6 centres. They had endured symptoms for a median of 8 years (range 2-20) and had undergone a median of 2 previous surgical procedures (range 1-3), including lateral sphincterotomy and anal dilatation. Anorectal physiological testing was performed on all patients who then underwent advancement anoplasty. The outcome was analysed retrospectively. Results. Pre-operative anorectal physiological testing showed a significantly lowered median maximal anal resting pressure of 42 mm Hg (range 12-72 mm Hg, normal range > 60 mm), P = 0.03. All patients underwent advancement anoplasty. At a median of seven months follow-up (range 2-22) seven of eight patients had healed their fissure and were asymptomatic. The median healing time was four months (range 2-6). Conclusion. Patients with chronic anal fissure, resistant to conventional therapy, may be successfully treated by advancement anoplasty. Healing time however, may be prolonged. In this series patients had a decreased anal resting pressure rather than anal hypertonia.

DRUG DESCRIPTORS:

glyceryl trinitrate--adverse drug reaction--ae; glyceryl trinitrate--drug therapy--dt; glyceryl trinitrate--topical drug administration--tp; analgesic agent--drug therapy--dt; analgesic agent--topical drug administration--tp; laxative--drug therapy--dt; diltiazem--adverse drug reaction--ae; diltiazem--drug therapy--dt; diltiazem--topical drug administration--tp; calcium channel blocking agent--adverse drug reaction --ae; calcium channel blocking agent--drug therapy--dt; calcium channel blocking agent--topical drug administration--tp; bethanechol--drug therapy --dt; botulinum toxin--drug therapy--dt

MEDICAL DESCRIPTORS:

*anus fissure--drug resistance--dr; *anus fissure--drug therapy--dt; *anus fissure--surgery--su; *anoplasty patient referral; symptom; disease duration; anus surgery; sphincterotomy; intestine function; treatment outcome; retrospective study; preoperative evaluation; anorectal pressure; rest; follow up; wound healing; time; conservative treatment; headache--side effect--si; human; male; female; clinical article; controlled study; aged; adult; article; priority journal

CAS REGISTRY NO.: 55-63-0 (glyceryl trinitrate); 33286-22-5, 42399-41-7 (diltiazem); 590-63-6, 674-38-4, 91609-06-2 (bethanechol)

SECTION HEADINGS:

- 009 Surgery
- 037 Drug Literature Index
- 038 Adverse Reaction Titles
- 048 Gastroenterology

5/9/8 (Item 2 from file: 73)
DIALOG(R) File 73:EMBASE
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07144725 EMBASE No: 1998033192
Pharmacologic therapy for anal fissure
Madoff R.D.
Dr. R.D. Madoff, University of Minnesota, St. Paul, MN 55114 United States
New England Journal of Medicine (NEW ENGL. J. MED.) (United States) 22
JAN 1998, 338/4 (257-259)
CODEN: NEJMA ISSN: 0028-4793
DOCUMENT TYPE: Journal; Editorial
LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 15

DRUG DESCRIPTORS:

*glyceryl trinitrate--adverse drug reaction--ae; *glyceryl trinitrate--clinical trial--ct; *glyceryl trinitrate--drug therapy--dt; *botulinum toxin a--clinical trial--ct; *botulinum toxin a--drug

therapy--dt; *botulinum toxin a--pharmacology--pd

MEDICAL DESCRIPTORS:

*anus fissure--diagnosis--di; *anus fissure--drug therapy--dt
clinical feature; bleeding; pain; disease association; crohn disease; anus
carcinoma; human immunodeficiency virus infection; laser doppler flowmetry;
anorectal pressure; drug effect; wound healing; headache--side
effect--si; human; clinical trial; double blind procedure; controlled study
; editorial; priority journal

CAS REGISTRY NO.: 55-63-0 (glyceryl trinitrate); 93384-43-1 (

botulinum toxin a)

SECTION HEADINGS:

- 037 Drug Literature Index
- 038 Adverse Reaction Titles
- 048 Gastroenterology

5/9/9 (Item

WEST Search History

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DATE: Tuesday, December 19, 2006

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<input type="checkbox"/>	L10	L9 same (botox or bottox or bta or bont or bonta or bont-a or botulin or botulinum or botulism or bontoxilysin or botox\$ or neurotoxin or clostridial or clostridium or clostridia or bna or dysport\$ or myobloc\$)	12
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<input type="checkbox"/>	L12	decubitus near5 ulcer	2544
<input type="checkbox"/>	L13	dermal near5 ulcer	1051
<input type="checkbox"/>	L14	(L14 or l13) same (botox or bottox or bta or bont or bonta or bont-a or botulin or botulinum or botulism or bontoxilysin or botox\$ or neurotoxin or clostridial or clostridium or clostridia or bna or dysport\$ or myobloc\$)	15
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<input type="checkbox"/>	L16	l10 not l11 not l16	128
<input type="checkbox"/>	L17	anticholinergic or (cholinergic near antagonist)	8743
<input type="checkbox"/>	L18	L18 and (l9 or l13 or l14)	206
<input type="checkbox"/>	L19	L18 same (l9 or l13 or l14)	0
<input type="checkbox"/>	L20	L18.clm. and (l9 or l13 or l14).clm.	0
<input type="checkbox"/>	L21	l19 not l17 not l11 not l12 not l15 not l10	199
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END OF SEARCH HISTORY

07144725 EMBASE No: 1998033192

Pharmacologic therapy for anal fissure

Madoff R.D.

Dr. R.D. Madoff, University of Minnesota, St. Paul, MN 55114 United States

New England Journal of Medicine (NEW ENGL. J. MED.) (United States) 22 JAN 1998, 338/4 (257-259)

CODEN: NEJMA ISSN: 0028-4793

DOCUMENT TYPE: Journal; Editorial

LANGUAGE: ENGLISH

NUMBER OF REFERENCES: 15

DRUG DESCRIPTORS:

*glyceryl trinitrate--adverse drug reaction--ae; *glyceryl trinitrate --clinical trial--ct; *glyceryl trinitrate--drug therapy--dt; *botulinum toxin a--clinical trial--ct; *botulinum toxin a--drug therapy--dt; *botulinum toxin a--pharmacology--pd

MEDICAL DESCRIPTORS:

*anus fissure--diagnosis--di; *anus fissure--drug therapy--dt clinical feature; bleeding; pain; disease association; crohn disease; anus carcinoma; human immunodeficiency virus infection; laser doppler flowmetry; anorectal pressure; drug effect; wound healing; headache--side effect--si; human; clinical trial; double blind procedure; controlled study ; editorial; priority journal

CAS REGISTRY NO.: 55-63-0 (glyceryl trinitrate); 93384-43-1 (botulinum toxin a)

SECTION HEADINGS:

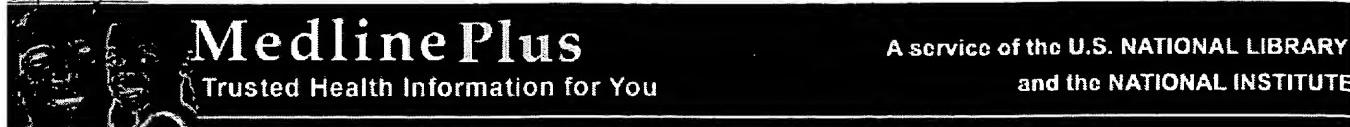
037 Drug Literature Index

038 Adverse Reaction Titles

048 Gastroenterology

08338374 Genuine Article#: 272YD Number of References: 38
Title: Rehabilitation after traumatic brain injury
Author(s): Barnes MP (REPRINT)
Corporate Source: UNIV NEWCASTLE UPON TYNE, HUNTERS MOOR REG NEUROREHABIL
CTR, ACAD UNIT NEUROL REHABIL, HUNTERS RD/NEWCASTLE UPON TYNE NE2
4NR/TYNE & WEAR/ENGLAND/ (REPRINT)
Journal: BRITISH MEDICAL BULLETIN, 1999, V55, N4, P927-943
ISSN: 0007-1420 Publication date: 19990000
Publisher: ROYAL SOC MEDICINE PRESS LTD, 1 WIMPOLE STREET, LONDON W1M 8AE,
ENGLAND
Language: English Document Type: ARTICLE
Geographic Location: ENGLAND
Subfile: CC LIFE--Current Contents, Life Sciences; CC CLIN--Current
Contents, Clinical Medicine;
Journal Subject Category: MEDICINE, GENERAL & INTERNAL
Abstract: Head injury is a common disabling condition but regrettably facilities for rehabilitation are sparse. There is now increasing evidence of the efficacy of a comprehensive multidisciplinary rehabilitation team compared to natural recovery following brain injury. This chapter outlines some basic concepts of rehabilitation and emphasises the importance of valid and reliable outcome measures. The evidence of the efficacy of a rehabilitation programme is discussed in some detail. A number of specific rehabilitation problems are outlined including the management of spasticity, nutrition, pressure ***sores***, and urinary continence. The increasingly important role of assistive technology is illustrated, particularly in terms of communication aids and environmental control equipment. However, the major long-term difficulties after head injury focus around the cognitive, intellectual, behavioural and emotional problems. The complex management of these disorders is briefly addressed and the evidence of the efficacy of some techniques discussed. The importance of recognition of the vegetative state and avoidance of misdiagnosis is emphasised. Finally, the important, but often neglected, area of employment rehabilitation is covered.
Identifiers--KeyWord Plus(R): UPPER EXTREMITY SPASTICITY; SEVERE
HEAD-INJURY; EARLY INTERVENTION; CONTROLLED TRIAL; BOTULINUM
TOXIN; FOLLOW-UP; RELATIVES; EFFICACY

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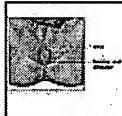
Anal fissure

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Illustrations

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Definition [Return to top](#)

An anal fissure is a small split or tear in the anal mucosa that may cause painful bowel movements and bleeding. There may be blood on the outside of the stool or on the toilet tissue following a bowel movement.

Causes, incidence, and risk factors [Return to top](#)

Anal fissures are extremely common in young infants but may occur at any age. Studies suggest 80% of infants will have had an anal fissure by the end of the first year. Most fissures heal on their own and do not require treatment, aside from good diaper hygiene. However, some fissures may require medical treatment.

The incidence of anal fissures decreases rapidly with age. Fissures are much less common among school-aged children than among infants.

In adults, fissures may be caused by constipation, the passing of large, hard stools, or by prolonged diarrhea. In older adults, anal fissures may be caused by decreased blood flow to the area.

Anal fissures are also common in women after childbirth and people with Crohn's disease.

Symptoms [Return to top](#)

- Pain while having a bowel movement
- Blood on the surface of stool (not mixed in with stool)
- Blood on toilet tissue or wipes
- A crack in the skin that is visible when the anus is stretched slightly (the fissure is almost always in the midline)
- Constipation, often with painful bowel movements

Signs and tests [Return to top](#)

- Inspection of the rectum
- Physical exam of the rectal mucosa

Treatment [Return to top](#)

- Stool softeners
- Dietary adjustment (addition of bulk -- substances that absorb water while in the intestinal tract)
- Cleansing more gently
- Petroleum jelly
- Sitz bath
- Anesthetic ointment, if pain interferes with normal bowel movement
- Topical muscle relaxants

These measures generally heal more than 90% of anal fissures.

For fissures that do not heal with these home treatments, injection of botulinum toxin (Botox) into the anal sphincter may be used to temporarily paralyze the anal sphincter muscle and promote healing. Another option for nonhealing fissures is a minor surgical procedure to relax the sphincter.

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Anal fissures generally heal quickly without residual problems. However, people who develop fissures are more likely to have them in the future.

Complications [Return to top](#)

Occasionally, a fissure becomes chronic and will not heal. Chronic fissures may require minor surgery to relax the sphincter.

Calling your health care provider [Return to top](#)

Call your health care provider if symptoms associated with anal fissure are present, or if the fissure does not heal appropriately with treatment.

Prevention [Return to top](#)

To prevent anal fissures in infants, be sure to change diapers frequently.

To prevent fissures at any age:

- Keep the anal area dry

- Wipe with soft materials or a moistened cloth or cotton pad
- Promptly treat any constipation or diarrhea
- Avoid irritating the rectum

Update Date: 7/14/2006

Updated by: J.A. Lee, M.D., Division of Surgery, UCSF, San Francisco, CA. Review provided by VeriMed Healthcare Network.



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Pharmacologic Therapy for Anal Fissure

It has been said that all patients with anorectal symptoms come to the doctor reporting hemorrhoids or worrying about cancer. Among the myriad other diagnostic possibilities, one of the most common is anal fissure. This small tear in the anal skin just at or inside the anal verge typically causes symptoms of severe pain after defecation and bright red rectal bleeding. Anal fissures are easy to diagnose by taking a history and performing an appropriate physical examination — visualizing a sentinel skin tag and everting the anal canal by opposing traction of the patient's buttocks — and easier still for the unsuspecting or inexperienced physician to miss. As in all acutely painful anal conditions, instrumentation generally produces far more discomfort for the patient than information for the physician and should be deferred until the fissure has healed.

Anal fissures are highly likely to occur in the midline, particularly posteriorly. Fissures off the midline raise the question of an underlying disorder, such as Crohn's disease, anal carcinoma, human immunodeficiency virus infection, or syphilis. Although typical fissures are commonly described as idiopathic, current evidence suggests that they are caused by high sphincter pressures and secondary local ischemia.

The anal-sphincter mechanism comprises the internal anal sphincter, the smooth-muscle termination of the rectal circular muscle layer that provides most of the anal canal's resting tone, and the external anal sphincter, a striated muscle under voluntary control. There is a relative deficiency of blood vessels in the posterior commissure of the anal canal of most people.¹ Laser Doppler flow studies document a parallel hypoperfusion of this area in normal subjects.² Patients with anal fissure typically have high resting anal pressures and infrequent spontaneous relaxation of the internal anal sphincter.³ Because the anodermal blood supply passes through the internal anal sphincter,¹ these high pressures can impede blood flow. Anodermal perfusion is particularly low at the base of fissures.²

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For many years treatment of anal fissure has focused on alleviating sphincter hypertonia. Conservative therapy, consisting of sitz baths, topical anesthetics, and the use of bulking supplements, aims to alleviate pain and dilate the sphincter with large, soft stools. Operative therapy decreases sphincter pressures either by forceful dilation (increasingly of historical interest only) or, now far more commonly, by lateral internal sphincterotomy. Although this technique is a simple and effective outpatient surgical procedure performed under local anesthesia, its fundamental drawback is its potential to cause minor but sometimes permanent alterations in the control of gas, mucus, and occasionally stool.^{4,5} This problem has motivated a quest for pharmacologic ways to create a temporary or reversible "sphincterotomy," one that would lower sphincter pressures only until the fissure had healed. Two such approaches have been identified.

There is now strong evidence that relaxation of the internal anal sphincter is mediated by the neurotransmitter nitric oxide.⁶ Various topical organic nitrate preparations have been used to induce internal-anal-sphincter relaxation in patients with chronic fissures. In a double-blind, randomized, placebo-controlled trial involving 80 patients, Lund and Scholefield documented a healing rate of 68 percent in patients treated with 0.2 percent nitroglycerin (glyceryl trinitrate), as compared with 8 percent in the placebo group.⁷ The maximal resting anal pressure decreased and anodermal blood flow increased in the treatment group but not in the placebo group. Fissures recurred in 8 percent of the successfully treated patients, but all the fissures healed with a second course of treatment. Schouten et al. reported similar results in an uncontrolled series of 34 patients with chronic fissure treated with topical 1 percent isosorbide dinitrate.⁸

One clinical problem with topical nitrate therapy is a substantial incidence of headache, particularly at higher drug concentrations.^{7,9} Fortunately, these headaches are often minor and transient. A second potential difficulty is the development of drug tolerance, a problem well documented with nitrate therapy for cardiovascular disease and now also reported during treatment for anal fissure.¹⁰

The other pharmacologic approach to anal fissure involves the use of botulinum toxin. Once again, the aim is to decrease the resting anal pressure, in this case by preventing the release of acetylcholine from presynaptic nerve terminals. More famous as a lethal poison, botulinum toxin has found its way into the therapy of a number of skeletal-muscle disorders, including strabismus, blepharospasm, and spasmodic torticollis.¹¹ Botulinum toxin has also been used for smooth-muscle disorders, including achalasia¹² and detrusor dysfunction.¹³ In this issue of the *Journal*, Maria and associates report the results of a double-blind, placebo-controlled study of botulinum toxin A in 30 patients with chronic anal fissure.¹⁴ Despite discrepancies in the randomization (more men and older patients in the control group), the results show a convincing therapeutic effect. After two months, 87 percent of the treated patients had symptomatic relief and 73 percent were healed, as compared with 27 percent and 13 percent, respectively, of the controls. Resting anal pressure decreased significantly in the treated patients but not in the controls. All four patients with initial treatment failure healed after retreatment, as did 70 percent of the controls who crossed over to botulinum-toxin injection. Scanty data are presented with respect to alterations in continence, but it appears that only one patient who received toxin suffered temporary flatus incontinence. Similar results were recently reported by Jost, who noted healing in 79 of 100 patients six

months after botulinum-toxin injection.¹⁵ Eight patients had early relapses, and seven had temporary gas or stool incontinence. In contrast to Maria et al., Jost used a smaller dose of toxin (2.5 to 5 units, vs. 20 units) and injected the toxin into the external sphincter rather than the internal sphincter.

Contradicting the adage that new drugs should be used rapidly before they lose their ability to heal, pharmacologic therapy with nitrates or botulinum toxin appears to be maintaining its early promise as a nonoperative option for patients with anal fissure. Yet a number of practical and theoretical questions remain unanswered. For nitrates: Which preparation should be used, at what concentration, and how often should it be applied? For botulinum toxin: What dose should be used, and where should it be injected — the internal or external sphincter? For both agents: Which works faster and with fewer adverse effects? How substantial is the problem of incontinence, and is it ever more than temporary? What are the relative costs? Finally, what are the long-term relapse rates? If the beauty of chemical sphincterotomy lies in its transience, how often will elevated sphincter pressures lead to recurrence months or years down the road?

Most patients with a newly diagnosed anal fissure should have an initial trial of conservative therapy, and the majority of patients with acute fissures will heal with such treatment alone. For patients for whom nonoperative treatment fails or for those who simply hurt too much to wait for its success, lateral internal sphincterotomy is usually the next step. Although a minority of patients do indeed experience minor and sometimes permanent decreases in continence after surgery, pain relief is almost immediate, patient satisfaction is high, and the long-term relapse rate is low. This simple approach has been challenged by the advent of pharmacologic therapy. For now, doctors can opt to include topical nitroglycerin as a component of conservative fissure therapy but must remember that commercially available preparations in the United States (2 percent solutions) are too strong and have to be diluted. Comparative trials and further long-term follow-up are needed to define the ultimate roles of botulinum toxin and topical nitrates in the treatment of anal fissure.

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Long-term Follow-up (42 Months) of Chronic Anal Fissure After Healing With Botulinum Toxin

MIGUEL MINGUEZ,* BELEN HERREROS,* ALEJANDRO ESPI,† EDUARDO GARCIA-GRANERO,† VICENTE SANCHIZ,* FRANCISCO MORA,* SALVADOR LLEDO,† and ADOLFO BENAGES*

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Background & Aims: Botulinum toxin is an effective treatment in idiopathic chronic anal fissure, but the long-term outcome after healing is not well documented. We analyzed the long-term outcome of patients in whom an anal fissure had healed after botulinum toxin injection and the factors contributing to recurrence. **Methods:** Fifty-seven patients who had completely healed 6 months after injection of botulinum toxin were reassessed every 6 months. The follow-up was 42 months in all patients. Clinical and manometric differences between the permanently healed and the relapsed group were statistically analyzed. **Results:** Four patients were lost to follow-up. A fissure recurrence was shown in 22 patients (41.5%). Statistical differences between the permanently healed and the relapsed group were detected when analyzing the anterior location of the fissure (6% vs. 45%), a longer duration of the disease (38% vs. 68%), the need for reinjection (26% vs. 59%), a higher total dose injected to achieve definitive healing (13% vs. 45%), and the percentage decrease of maximum squeeze pressure after injection (-28% vs. -13%; $P < 0.05$). **Conclusions:** The late recurrence rate of chronic anal fissure is high when the effect of botulinum toxin disappears. The highest risk of recurrence is associated with anterior location of the anal fissure, prolonged illness, the need for reinjection and for high doses to achieve healing, and a lower decrease of maximum squeeze pressure after treatment.

Idiopathic anal fissure is a frequent condition, afflicting in most cases an adult population with otherwise healthy status. A defecatory anal pain out of proportion to the size of the lesion is the usual complaint of these patients. Lateral internal sphincterotomy, a simple outpatient surgical procedure, offers permanent relief in more than 95% of patients.¹⁻³ However, different degrees of fecal incontinence may arise immediately or years after the sphincterotomy, leading occasionally to a serious disturbance in the quality of life.^{4,5} Although permanent continence disorders are not the rule, Nyam and Pemberton⁶ recently stressed the magnitude of this complication, reporting that 45% of their patients rec-

ognized some degree of incontinence sometime after surgery. A quest for reversible weakening methods of the internal sphincter has been undertaken to avoid this drawback. Two of these approaches (botulinum toxin injection and nitroglycerine ointments), which promote a temporary decrease of anal pressures that frequently allows fissures to heal, have been widely accepted.⁷

Results of long-term follow-up of patients treated with nitroglycerine ointments and botulinum toxin injections are lacking. Few studies have dealt, up to now, with the natural evolution of a nonoperated chronic fissure, and it seems important to determine whether early successful results of these new modalities can be indefinitely sustained. A significant recurrence rate of healed fissures after topical nitroglycerine therapy has been described in a recent study with a median follow-up of 9 months.⁸ Kennedy et al.⁹ were able to assess clinically and manometrically the long-term outcome of a cohort of 17 patients treated with glyceryl trinitrate ointment, and the recurrence rate of those who had healed was 62.5% after a mean follow-up of 28.5 months. In contrast, Maria et al.,¹⁰ using botulinum toxin, found no relapse in healed patients with a mean follow-up of 24 months.

The aim of our study was to analyze the long-term outcome of a group of patients in whom an anal fissure had healed 6 months after botulinum toxin injection. The pattern and rate of fissure recurrence with this conservative approach, as well as the factors contributing to recurrence, were also evaluated.

Materials and Methods

Inclusion Criteria

From December 1995 to May 1997, 69 patients with chronic idiopathic anal fissure underwent a modality of therapy with anal intraspincteric injection of botulinum toxin (BOTOX A; Allergan Pharmaceuticals, Irvine, CA) at our insti-

tution. All patients reported postdefecatory anal pain for at least 2 months, and clinical signs of chronicity were evident at inspection. Unsuccessful conservative treatments (warm sitz baths, bulk laxatives, and local anesthetic gels) were always undertaken before inclusion. No topical glyceryl trinitrate ointments were used. Patients with acute or complicated fissures (stenosis, abscess, fistula, or hemorrhoids); those with associated conditions (acquired immunodeficiency syndrome, sexually transmitted disease, inflammatory bowel disease, tuberculosis, or leukemia); those who were pregnant; and those receiving coumarin therapy were excluded. Fifty-seven patients out of those initially treated, who were regarded as completely healed 6 months after treatment, were included in this study. There were 28 women and 29 men; the median age was 46 years (range, 23–69 years).

Treatment Methods and Manometric Study

The injection was applied through the intersphincteric groove into the internal sphincter, always with a final concentration of 2.5 U/0.1 mL. The initial dose injected was different along the period of the study, as we reported previously.¹¹ Five units of diluted botulinum toxin was injected into each side of the anal sphincter close to both lateral midpoints in 19 patients (total dose, 10 U). In 21 patients, an additional 5-U dose was injected below the fissure, just into the internal sphincter (total dose, 15 U). Finally, 17 patients received a 7-U dose injection into each side of the sphincter and below the fissure (total dose, 21 U). Rejection between 1 and 3 months after the initial dose was performed in those patients who did not clinically improve or showed persistence of the fissure at inspection. The dose of the re-injection was the same as the initial dose. Twenty-three patients had to be re-injected to achieve complete healing. Anal pain, bleeding, and defecatory difficulty had been initially assessed by using analog scores, as previously described.¹¹ Anorectal manometry was performed with a low-compliance water perfusion system (Arndorfer Medical Specialties, Inc., Greendale, WI) with a 4-lumen catheter (external diameter, 4 mm) that had radially arranged ports in cross-section. Pressures were recorded by means of a pressure transducer (1280 C; Hewlett-Packard, Avondale, PA) situated within each infusion line and connected via amplifiers to a chart recorder (8805 C; Hewlett Packard). With the patient in the left lateral position and the hips flexed to 90°, the catheter (lubricated lightly with water-soluble gel) was inserted into the rectum, so that the manometric holes were situated 6 cm from the anal verge. After a 60-second delay, the catheter was withdrawn from the rectum in 0.5-cm steps, remaining for at least 1 minute at each station to ensure that pressure there had reached a plateau; the patient was then asked to squeeze maximally. Maximum anal resting pressure and maximum squeeze pressure, obtained as the maximal voluntary anal contraction related to basal rectal pressure, were measured before and 1 month after treatment.

Follow-up

All patients were advised to follow healthy dietary habits, particularly those including a high fiber content. All these patients completed a follow-up of 42 months from the starting point of evaluation (6 months after treatment). Every 6 months, patients were reassessed to rule out fissure recurrence, whereas those who in the meantime were symptomatic were immediately evaluated. In this way, 2 groups have been constituted throughout the study, with fissure recurrence as the classifier.

Statistical Analysis

Differences between these 2 groups regarding age, sex, duration of symptoms, fissure location at the anal verge, presence of anal tags, history of previous anal surgery, and defecatory habits were evaluated. Clinical and manometric differences were also evaluated, including pain, bleeding and defecatory difficulty, resting and squeeze anal pressures before and 1 month after treatment, and, finally, the need for re-injection during the first 6 months after injection. The initial dose of toxin injected and the total dose used during the first 6 months of treatment were also included as a variable between the groups. Statistical analyses were performed to identify independent variables related to fissure recurrence by means of the χ^2 method for qualitative parameters and the Student *t* test for quantitative ones. Conditions independently influencing fissure recurrence were assessed by multiple logistic regression. Values of $P < 0.05$ were always regarded as statistically significant.

Results

Four patients (7%) were lost to follow-up at the end of the study. A fissure recurrence during the 4 years of evaluation was shown in 22 patients (41.5%). The patients with recurrence within each 6 months of follow-up are shown in Table 1. In 3 patients, the relapsed fissure was located at a different site of the anus, whereas the other 19 had a new fissure at the same location as the first. Nine of these 22 patients related the onset of this new fissure to an acute episode of constipation, concurrent with desiccated feces and excessive straining. A double recurrence was detected in 3 patients, all of whom

Table 1. Cumulative Recurrence Rates at 6-Month Intervals

Follow-up (mo)	No. patients with recurrence	Cumulative recurrence (%)	Lost to follow-up (<i>n</i>)
6–12	6	6/56 (10.7)	1
13–18	8	14/55 (25.4)	0
19–24	4	18/54 (33.3)	1
25–30	1	19/53 (35.8)	2
31–36	2	21/53 (39.6)	0
37–42	1	22/53 (41.5)	0
43–48	0	22/53 (41.5)	0

Table 2. Relationship Between Recurrence and Clinical Parameters

Clinical parameter	No recurrence (n = 31)	Recurrence (n = 22)
Mean age, yr (mean ± SD)	44 ± 13	46 ± 14
Sex (M/F ratio)	17/14	8/14
Duration of symptoms ≥12 mo	11/29 (37.9%)	15/22 (68.2%) ^a
Previous anal surgery	3/31 (9.7%)	2/22 (9.1%)
Anal tag	11/31 (35.5%)	13/22 (59.1%)
Anterior fissure	2/31 (6.5%)	10/22 (45.5%) ^a
Reinjection	8/31 (25.8%)	13/22 (59.1%) ^a
Total dose >21 U of BT	4/31 (12.9%)	10/22 (45.5%) ^a

U, international units of diluted botulinum toxin; BT, botulinum toxin.

^aP < 0.05.

were women with anteriorly located fissures. One patient improved significantly each time (24 and 42 months after toxin injection) with conservative treatment. Another one underwent surgery, but her fissure recurred again because of incomplete sphincterotomy; finally, the last one initially did well with conservative measures, but 2 years later she had to be referred to surgery because of a new recurrence. In summary, 12 patients of the recurrence group were operated on, 2 were successfully reinjected with botulinum toxin, and, finally, the other 8 improved with medical treatment. Lateral internal sphincterotomy was performed on an additional patient because of persistence of symptoms, but in this last case a fissure recurrence had not ensued.

When clinical characteristics before the initial course of therapy were analyzed, only anterior location of the fissure and duration of the disease of longer than 12 months were clearly associated with fissure recurrence (Table 2). The percentages of episodes of anal bleeding on defecation and clinical scores of pain, bleeding, and defecatory difficulty 6 months after toxin injection were higher in the recurrence group (Mann-Whitney *U* test; *P* < 0.05). Ten of 12 patients (83.3%) with an anterior located fissure developed late recurrence, whereas only 12 of 41 (29.3%) with posterior fissure did so (*P* < 0.05). This also means that 45.4% of the patients with recurrence had previously had an anteriorly located fissure. No relationship between the location of the first fissure and the onset of recurrence during follow-up was shown. Clinical parameters such as age, sex, anal tag, previous anal surgery, and pain score were not related to the location of the fissure. Only the percentage of bleeding episodes related to the passage of stools was significantly higher in patients with anterior fissures (35.5% anterior fissure vs. 24.5% posterior fissure; *P* < 0.05). Maximum resting anal pressure and maximum squeeze pressure decreased significantly after treatment in patients with posterior fissures (pretreatment 110.95 ± 31 mm Hg

and posttreatment 101.7 ± 27 mm Hg, pretreatment 239.58 ± 88 mm Hg and posttreatment 174.6 ± 58 mm Hg; *P* < 0.05 and *P* < 0.001, respectively). In patients with anterior fissures, only squeeze pressure decreased significantly after injection (pretreatment 182.2 ± 63 mm Hg; posttreatment 145.9 ± 5 mm Hg; *P* < 0.05).

The need for reinjection to achieve definitive healing of the fissure in the first 6 months after treatment was also significantly higher in the recurrence group (13 of 22 [59.1%] vs. 8 of 31 [25.8%]; *P* < 0.05). Thirteen patients of the 21 (61.9%) who were reinjected had fissure recurrence, and only 9 of the 32 (28.1%) who had healed with a single course of treatment relapsed (*P* < 0.05). The mean total amount of botulinum toxin injected was similar in both groups, but the number of patients who needed more than 21 U to achieve healing was higher in the recurrence group (*P* < 0.05).

When we analyzed the initial dose injected, no significant differences among groups were detected according to the recurrence rate (dose 10 U, 6 of 17 [35.3%]; dose 15 U, 9 of 19 [47.4%]; dose 21 U, 7 of 17 [41.2%]; *P* > 0.05) or the need for reinjection (dose 10 U, 9 of 17 [52.9%]; dose 15 U, 5 of 19 [26.3%]; dose 21 U, 7 of 17 [41.2%]; *P* > 0.05). Neither was the location of the fissure at the anal verge significantly different among the groups of initial dose injected (anterior location in 17.6% [dose 10 U], 26.3% [dose 15 U], and 23.5% [dose 21 U]; *P* > 0.05). Only the decrease of the mean of the maximum squeeze pressure after treatment was significantly higher in the group of patients initially treated with 21 U of botulinum toxin (dose 10 U, 16.7 ± 4.6 mm Hg; dose 15 U, 19.2 ± 4.1 mm Hg; dose 21 U, 32.8 ± 19.3 mm Hg; *P* = 0.045). When we analyzed the presence of recurrence, no differences between groups were detected when we analyzed anal pressures before treatment—both maximum resting pressures (107.2 ± 35 mm Hg vs. 113.5 ± 27 mm Hg; *P* > 0.05) and maximum squeeze pressures (242.9 ± 97 mm Hg vs. 205.85 ± 63 mm Hg; *P* > 0.05).

A significant decrease of maximum resting pressure and maximum squeeze pressure was detected 1 month after toxin injection only in the permanently healed group. In both groups, the mean maximum voluntary contraction decreased significantly 1 month after treatment, but the level of significance of this drop was higher in the group of patients who later did well (Table 3). The percentage decrease of squeeze pressure after treatment was also significantly higher in this group of patients (28% vs. 13%; *P* < 0.05; Figure 1). Finally, the most important risk factors for recurrence, as obtained by a

Table 3. Relationship Between Recurrence and Manometric Findings

Variable	MRP (mm Hg)		MSP (mm Hg)	
	Basal	After treatment	Basal	After treatment
No recurrence	107.2 ± 35	95.2 ± 25*	242.9 ± 97	165.2 ± 56*
Recurrence	113.5 ± 27	103.4 ± 25	205.8 ± 63	174.3 ± 61*

NOTE: Figures are mean ± SD. MRP, maximum resting pressure; MSP, maximum squeeze pressure.

* $P < 0.05$, paired Student *t* test.

** $P < 0.001$, paired Student *t* test.

forward stepwise multiple logistic regression model, were anterior location of the fissure, duration of the initial disease of longer than 12 months, the need for a total dose higher than 21 U of botulinum toxin, and the percentage change of maximum squeeze pressure after injection (Table 4).

Discussion

In recent years, there has been a great advance in treating chronic anal fissure via the introduction of new types of therapy that aim to achieve the beneficial results of surgery without adverse effects. These techniques are directed at chemically denervating the anal sphincter, and one of the most interesting to date is botulinum toxin injection, because studies of its effectiveness show healing of better than 80% and the absence of significant adverse effects.¹⁰⁻¹²

Nevertheless, the long-term history of chronic anal fissure after healing by means of this new nonsurgical modality is not well documented. Few studies assess long-term recurrence, and their follow-up periods are short and heterogeneous. Jost,¹³ in a prospective study of 100 patients treated with botulinum toxin, observed an 8% recurrence rate after 6 months' follow-up. Another group has not found any late fissure recurrence in patients successfully treated with botulinum toxin injec-

Table 4. Parameters Related to Recurrence (Logistic Regression Analysis)

Variable	OR	95% CI	P Value
Total dose >21 U	16	1.8-136.8	0.01
Length of disease ≥12 mo	11	1.5-94.4	0.01
Anterior location	23	1.7-327	0.01
% Change of MSP	1.1	1.1-1.12	0.01

U, international units of botulinum toxin; MSP, maximum squeeze pressure; OR, odds ratio; CI, confidence interval.

tion after different periods, but the longest average follow-up of these series was 24 months.^{10,14,15}

Our results show a recurrence rate of 41.5% in a follow-up period of 42 months, which is quite different from those mentioned previously, and our starting point of evaluation is different compared with other groups because it started 6 months after treatment. These differences could have arisen because our study is the only one to analyze the outcome of a homogeneous group of patients healed by botulinum toxin treatment through a uniform follow-up period (42 months). A complete absence of recurrence from using pharmacological treatment, with transitory effect, on a recurring chronic pathology seems questionable. In this regard, therapeutic procedures on chronic anal fissure, whether by drugs or sphincterotomy, always show a number of recurrences after healing. High rates of fissure recurrence have been reported in several studies assessing the long-term outcome of patients treated with local administration of nitrates. Recurrence rates of 62.5% and 46% have been found after an average follow-up of 28.5 and 15 months, respectively.^{9,16} In addition, surgical treatment that permanently removes the internal sphincter hypertonia has long-term recurrence rates from 1% to 3% in most series,¹⁻³ supporting the hypothesis that no current treatment of chronic anal fissure leads to a permanent cure for 100% of patients.

The high long-term recurrence rate after botulinum toxin treatment is not surprising. It could be related to the temporary effect of the toxin and also to the natural history of the disease. Although the latter issue is not well-known for nonsurgically treated chronic anal fissures, some studies show that these fissures rarely heal spontaneously and that the long-term recurrence rate may reach 50% after conservative treatment.¹⁷ In concordance with our series data, we found that 8 patients who relapsed after treatment with botulinum toxin healed later with conservative measures.

Other methodological aspects, such as the clinical profile of patients and differences regarding the injection procedure, could partially explain some differences observed between the groups in which botulinum toxin

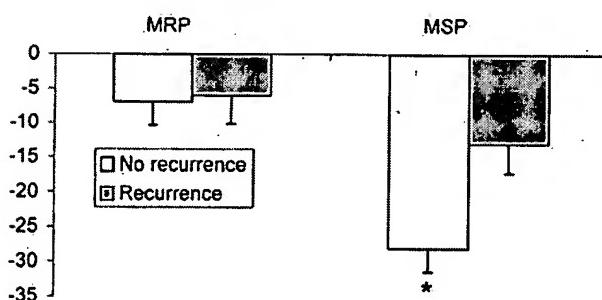


Figure 1. Percentage change of maximum resting pressure (MRP) and maximum squeeze pressure (MSP) 1 month after botulinum toxin injection (mean ± SEM; * $P < 0.05$).

injection has been assayed. Maria et al.^{10,14} and Brisinda et al.¹⁵ applied very restrictive inclusion criteria, excluding patients with anteriorly located fissures and patients with previous anal surgery. They also used higher doses and concentrations of toxin than others.

When clinical factors related to recurrence were analyzed in our study, some clinical parameters, such as anterior fissures and prolonged evolution of the disease, had a significant relationship with long-term recurrence. Identification of these clinical factors before treatment could help in the selection of patients in whom this treatment could be useful. A longer duration of disease was clearly associated with fissure recurrence, as has been recently reported by another group.¹⁶

With respect to fissure location, we observed recurrence in most patients with anterior chronic anal fissure (10 of 12; 83%), and approximately half of all recurrences occurred in these patients. Nevertheless, we were not able to show a relationship between the location of the lesion and clinical parameters such as sex, age, anal tag, previous anal surgery, or the scale of symptoms. However, bleeding episodes associated with defecation were more frequent in patients with anteriorly located fissures.

Although the cause of chronic anal fissures remains unclear, it is known that the anal verge shows anatomic and functional differences between areas. It has been documented that vascular perfusion in the posterior commissure is lower than in the anterior.^{18,19} Taylor et al.²⁰ showed that anal pressures are not symmetrical at the anal verge but that anterior pressures are higher in the distal anal canal, and they hypothesized that deficient posterior pressure provides less mucosal support and predisposes to the development of fissures. Keck et al.²¹ observed cross-sectional pressure profiles in patients with chronic fissure that were similar to those in healthy controls. However, we think that differences between areas at the anal verge do not seem to be related to the high recurrence rate of anterior fissures. Regarding manometric parameters, patients without recurrence had a greater decrease in anal resting pressure and squeeze pressure after treatment than those who later developed recurrence during follow-up. The failure to achieve pressure reduction after treatment is related to a lack of permanent healing, because temporary paresis of the anal sphincter has not been achieved in these patients.^{10,11} Permanent high anal pressures, once the effect of botulinum toxin on the anal sphincter decreases, tend to enhance fissure recurrence. Similar results have been found with botulinum toxin injection for achalasia, with

recurrences of 1 in 3 after 3 months and 2 in 3 after 1 year.²²

Although the injection of botulinum toxin was performed through the intersphincteric space, trying to reach the internal sphincter, our manometric results indicate that the pharmacological effect of botulinum toxin was mainly achieved on the external anal sphincter. This result is not surprising according to the available literature. It is very difficult to selectively puncture the internal anal sphincter because of its small thickness and the proximity of the external anal sphincter.¹² In 8 healthy volunteers, Schäfer et al.²³ described by endoanal ultrasonography a mean thickness of 1.9 ± 0.6 mm for the internal anal sphincter and 6.3 ± 1.0 mm for the external anal sphincter. Therefore, the reduction of the maximum squeeze pressure after injection may be due to the diffusion of botulinum toxin into the external anal sphincter because of the short distance from one sphincter to the other.

Differences between our manometric results and those of Maria et al.^{10,14} and Brisinda et al.¹⁵ could be explained by the different dilution of botulinum toxin we used (25 vs. 50 U/mL) and by the different overall methodology used for manometric evaluation of the maximum squeeze pressure. Squeeze pressure was obtained in our study as the maximum voluntary anal contraction related to basal rectal pressure, whereas Maria et al. reported it as the maximum voluntary contraction related to the pressure increase during squeezing over the resting anal pressure. Botulinum toxin can induce its blocking effect on both anal sphincters, and therefore squeeze anal pressure should not be obtained as a difference between squeeze and resting anal pressure in evaluating conditions that can affect both muscles.

Patients with posterior anal fissure show a significant decrease in both maximum resting pressure and squeeze pressure after treatment. However, patients with anterior fissure show a significant decrease only in maximum squeeze pressure. Thus, the failure to decrease anal resting pressure associated with anterior fissures could be related to the higher recurrence rate of those patients. A need for reinjection also suggests a lower tendency toward healing of the fissure, so this finding could be related to the likelihood of recurrence of these patients.

To conclude, the recurrence rate of chronic anal fissure healed by botulinum treatment is high at long-term follow-up, with more new cases developing in early periods. The highest risk of recurrence is associated with anterior location, prolonged period of illness, need for reinjection and for high doses to achieve healing, and a lower decrease of maximum squeeze pressure after treat-

ment. The meaning of the association between long-term recurrence of anal fissure and the anterior location at the anal verge is unknown. The high percentage of long-term recurrences is not surprising; it is consistent with the temporary pharmacological effect of botulinum toxin and with the natural history of the disease. Treatment of chronic anal fissure must be individualized, and local injection of botulinum toxin is an effective option in a high percentage of cases. Although its success is less than that of surgery, it is a valid option for patients who risk developing anal incontinence. More studies are needed to determine both the method of administering this treatment (dose injected, concentration, and location of the injection) and the clinical profile of patients who can benefit from this treatment vs. surgery.

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Received February 28, 2002. Accepted April 8, 2002.

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13823437 PMID: 12105839

Long-term follow-up (42 months) of chronic anal fissure after healing with ***botulinum*** toxin.

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Gastroenterology (United States) Jul 2002, 123 (1) p112-7, ISSN 0016-5085--Print Journal Code: 0374630

Publishing Model Print; Comment in Gastroenterology. 2003 Apr;124(4) 1165 ; Comment in PMID 12671920

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

Subfile: AIM; INDEX MEDICUS; Toxbib

BACKGROUND & AIMS: Botulinum toxin is an effective treatment in idiopathic chronic anal fissure, but the long-term outcome after healing is not well documented. We analyzed the long-term outcome of patients in whom an anal fissure had healed after botulinum toxin injection and the factors contributing to recurrence. **METHODS:** Fifty-seven patients who had completely healed 6 months after injection of botulinum toxin were reassessed every 6 months. The follow-up was 42 months in all patients. Clinical and manometric differences between the permanently healed and the relapsed group were statistically analyzed. **RESULTS:** Four patients were lost to follow-up. A fissure recurrence was shown in 22 patients (41.5%). Statistical differences between the permanently healed and the relapsed group were detected when analyzing the anterior location of the fissure (6% vs. 45%), a longer duration of the disease (38% vs. 68%), the need for reinjection (26% vs. 59%), a higher total dose injected to achieve definitive healing (13% vs. 45%), and the percentage decrease of maximum squeeze pressure after injection (-28% vs. -13%; P < 0.05). **CONCLUSIONS:** The late recurrence rate of chronic anal fissure is high when the effect of ***botulinum*** toxin disappears. The highest risk of recurrence is associated with anterior location of the anal fissure, prolonged illness, the need for reinjection and for high doses to achieve healing, and a lower decrease of maximum squeeze pressure after treatment.

Tags: Female; Male

Descriptors: *Botulinum Toxins--therapeutic use--TU; *Fissure in Ano--drug therapy--DT; Adult; Aged; Botulinum Toxins--administration and dosage--AD; Chronic Disease; Dose-Response Relationship, Drug; Fissure in Ano--physiopathology--PP; Follow-Up Studies; Humans; Injections; Middle Aged; Pressure; Recurrence; Retreatment; Wound Healing--drug effects--DE

CAS Registry No.: 0 (Botulinum Toxins)

Record Date Created: 20020709

Record Date Completed: 20020816

pressure point

A cutaneous locus having pressure-sensitive elements which when compressed, pressure is appreciated.

(05 Mar 2000)

Previous: [pressure palsy](#), [pressure paralysis](#), [pressure plethysmograph](#), [pressure pneumothorax](#)

Next: [pressure reversal](#), [pressure sense](#), [pressure sore](#), [pressure stasis](#)

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DOCUMENT-IDENTIFIER: US 20050142102 A1

TITLE: Methods of treating neurological conditions with hematopoietic growth factors

Summary of Invention Paragraph:

[0015] Parkinson's disease is the most frequent movement disorder, with approximately 1 million patients in North America; about 1 percent of the population over the age of 65 years is affected. The core symptoms of the disease are rigor, tremor and akinesia (Adams et al., Principles of Neurology, 6.sup.th ed., New York, pp 1090-1095). The etiology of Parkinson's disease is not known. Nevertheless, a significant body of biochemical data from human brain autopsy studies and from animal models points to an ongoing process of oxidative stress in the substantia nigra, which could initiate dopaminergic neurodegeneration. Oxidative stress, as induced by the neurotoxins 6-hydroxydopamine and MPTP (N-methyl-1-4-phenyl-1,2,3,6-tetrahydropyridine), has been used in animal models to investigate the process of neurodegeneration. Although a symptomatic therapy exists (e.g. L-DOPA plus a decarboxylase inhibitor; bromocriptine, pergolide as dopamin agonists; and anticholinergic agents such as trihexyphenidyl (artane)), there is a clear need for a causative therapy, e.g. a neuroprotective therapy, that really halts the disease progress. These animal models have been used to test the efficacy of radical scavengers, iron chelators, dopamine agonists, nitric oxide synthase inhibitors and certain calcium channel antagonists. Apoptotic mechanisms are clearly operative in the animal models as well as in the patient (Mochizuki, et al. (2001), Proc. Natl. Acad. Sci. USA, 98, 10918-23, Xu et al. (2002), Nat. Med., 8, 600-6, Viswanath, et al. (2001), J. Neurosci., 21, 9519-28, Hartmann, et al. (2002), Neurology, 58, 308-10). This pathophysiology with involvement of oxidative stress and apoptosis also places Parkinson's disease amongst the other neurodegenerative disorders and stroke.

Summary of Invention Paragraph:

[0039] Spinal cord injury (SCI) occurs when a traumatic event results in damage to cells within the spinal cord or severs the nerve tracts that relay signals up and down the spinal cord. The most common types of SCI include contusion (bruising of the spinal cord) and compression (caused by pressure on the spinal cord). Other types of injuries include lacerations (severing or tearing of some nerve fibers, such as damage caused by a gun shot wound), and central cord syndrome (specific damage to the corticospinal tracts of the cervical region of the spinal cord). Severe SCI often causes paralysis (loss of control over voluntary movement and muscles of the body) and loss of sensation and reflex function below the point of injury, including autonomic activity such as breathing and other activities such as bowel and bladder control. Other symptoms such as pain or sensitivity to stimuli, muscle spasms, and sexual dysfunction may develop over time. SCI patients are also prone to develop secondary medical problems, such as bladder infections, lung infections, and bed sores. While recent advances in emergency care and rehabilitation allow many SCI patients to survive, methods for reducing the extent of injury and for restoring function are still limited. Immediate treatment for acute SCI includes techniques to relieve cord compression, prompt (within 8 hours of the injury) drug therapy with corticosteroids such as methylprednisolone to minimize cell damage, and stabilization of the vertebrae of the spine to prevent further injury. The types of disability associated with SCI vary greatly depending on the severity of the injury, the segment of the spinal cord at which the injury occurs, and which nerve fibers are damaged.

Detail Description Paragraph:

[0474] The best-characterized model of Parkinson's Disease (PD) has been developed by using the neurotoxin 1-methyl-4phenyl-1,2,3,6-tetrahydropyridine (MPTP). To study the efficacy of GCSF in the Parkinson model, we administrated MPTP in eight-week-old male mice. Each group of mice (n=15) was given a repeated i.p. injection of MPTP-HCl or saline (once daily for 5 consecutive days at a concentration of 30 mg/kg, 5 ml/kg) and a repeated s.c. (once daily, for 22 consecutive days) administration of buffer, GCSF (0.03 mg/kg; 5 ml/kg) or minocycline (45 mg/kg; 5 ml/kg). While the first application of GCSF was performed immediately after MPTP (or saline for group 0), minocycline

was administrated 30 minutes thereafter, because of possible interactions of both compounds. All animals of each group were sacrificed at day 22. Until that time, mice were analyzed both for locomotor activity (accelerating RotaRod) and body weight was determined daily. Furthermore each brain is subjected to a HPLC analysis with electrochemical detection for measuring the concentration of dopamine, 3,4-Dihydroxyphenylacetic acid (DOPAC) and the Homovanilic acid (HVA) in the striatum and nucleus accumbens.

Detail Description Paragraph:

[0482] One additional model for studying efficacy of the hematopoietic factors for Parkinson's disease is the 6-OHDA model. This model is based upon the injection of 6OHDA directly into the substantia nigra or into the striatum. The drug selectively accumulates in dopaminergic neurons and leads to the apoptosis of these cells. In rats, 6OHDA is an effective neurotoxin that has been predominantly used to produce unilateral lesions. The extent of dopamine depletion can be assessed by examining rotational behaviour in response to amphetamine or apomorphine (Ungerstedt 1971). The easily and good quantifiable motor deficit constitutes a major advantage of this model. Additionally to the behaviour parameter the striatal level of tyrosine hydroxylase (TH) positive neurons after immunohistochemistry and the level of dopamine and its metabolites after a HPLC analysis can also be determined. The 6OHDA can be used to ascertain the efficacy of GCSF and GMCSF in a PD rat model. Adult Sprague-Dawley rats (body weight 250 g) are unilateral lesioned after one stereotaxic injection of 8 .mu.g in 2 .mu.l 6OHDA in the substantia nigra or in the striatum. Different doses of GCSF (0.03 mg/kg; 0.1 mg/kg, or others) can be administrated subcutaneously daily immediately after the lesioning for 2 weeks. Other groups of treated animals receive a single dose of intrastriatal or intranigral GCSF, or GMCSF (300 .mu.g/kg) immediately after the injection of 6OHDA. As for the MPTP model study minocycline can be used as a neuroprotective reference compound (45 mg/kg once daily s.c.). Sham animals and lesioned animals treated with buffer are used as control groups. Two weeks after lesioning animals are subjected to rotational behaviour testing. Rats are injected s.c. with apomorphine, placed in a bowl cage and the number of contralateral rotations over a 1 h period are recorded. Numbers of rotations for each animal group are compared using standard statistical tests. After the behavioural testing, animals are killed and the brains are processed to for immunochemistry to assay the total number of TH-positive neurons and for HPLC for determining the level of dopamine.

10963374 PMID: 8772071

The management of chronic fissure in-ano with ***botulinum*** / toxin.
Mason P F; Watkins M J; Hall H S; Hall A W
Department of Surgery, Glenfield General Hospital, Leicester, UK.
Journal of the Royal College of Surgeons of Edinburgh (ENGLAND) Aug
1996, 41 (4) p235-8, ISSN 0035-8835--Print Journal Code: 7503110
Publishing Model Print; Comment in J R Coll Surg Edinb. 1997
Aug;42(4):288-9; Comment in PMID 9276578; Comment in J R Coll Surg Edinb.
1997 Aug;42(4):289; Comment in PMID 9276579; Comment in J R Coll Surg
Edinb. 1997 Aug;42(4):289-90; Comment in PMID 9276580

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

Subfile: INDEX MEDICUS; Toxbib

Five patients with a chronic fissure in-ano each received an injection of Clostridium botulinum type A toxin into the lower internal anal sphincter. A mean lowering of maximum resting anal pressure by 23.3 (SEM 5.6) cm H₂O was achieved within seven days. Maximum voluntary squeeze pressures were not significantly altered. Anal compliance increased in all cases. Healing of the fissure with an apparent reduction in anal sensation occurred in three of the patients and partial resolution of symptoms in the other two. No adverse effects resulted from injections of the toxin. A controlled trial to compare the relative efficacies of botulinum toxin and lateral sphincterotomy is required.

Tags: Male

Descriptors: *Botulinum Toxins--therapeutic use--TU; *Cholinergic Antagonists--therapeutic use--TU; *Fissure in Ano--therapy--TH; Adult; Aged; Anal Canal--drug effects--DE; Anal Canal--physiopathology--PP; Anal Canal--radiography--RA; Barium Sulfate--diagnostic use--DU; Botulinum Toxins--administration and dosage--AD; Cholinergic Antagonists--administration and dosage--AD; Chronic Disease; Comparative Study; Contrast Media; Controlled Clinical Trials; Defecation; Electromyography; Enema; Fissure in Ano--physiopathology--PP; Fissure in Ano--radiography--RA; Fissure in Ano--surgery--SU; Humans; Injections; Middle Aged; Muscle Contraction--drug effects--DE; Pressure; Sensation; Wound

Healing

CAS Registry No.: 0 (Botulinum Toxins); 0 (Cholinergic Antagonists); 0 (Contrast Media); 7727-43-7 (Barium Sulfate)

Record Date Created: 19961024

Record Date Completed: 19961024

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L20: Entry 13 of 56

File: PGPB

Dec 1, 2005

DOCUMENT-IDENTIFIER: US 20050267062 A1

TITLE: Regulation of angiogenesis with zinc finger proteins

Detail Description Paragraph:

[0273] Toxin molecules also have the ability to transport polypeptides across cell membranes. Often, such molecules are composed of at least two parts (called "binary toxins"): a translocation or binding domain or polypeptide and a separate toxin domain or polypeptide. Typically, the translocation domain or polypeptide binds to a cellular receptor, and then the toxin is transported into the cell. Several bacterial toxins, including Clostridium perfringens iota toxin, diphtheria toxin (DT), Pseudomonas exotoxin A (PE), pertussis toxin (PT), Bacillus anthracis toxin, and pertussis adenylate cyclase (CYA), have been used in attempts to deliver peptides to the cell cytosol as internal or amino-terminal fusions (Arora et al., J. Biol. Chem., 268:3334-3341 (1993); Perelle et al., Infect. Immun., 61:5147-5156 (1993); Stenmark et al., J. Cell Biol. 113:1025-1032 (1991); Donnelly et al., PNAS 90:3530-3534 (1993); Carbonetti et al., Abstr. Annu. Meet. Am. Soc. Microbiol. 95:295 (1995); Sebo et al., Infect. Immun. 63:3851-3857 (1995); Klimpel et al., PNAS U.S.A. 89:10277-10281 (1992); and Novak et al., J. Biol. Chem. 267:17186-17193 (1992)).

Detail Description Paragraph:

[0308] Wound treatment is another general type of application in which administration of the ZFPs, nucleic acids and compositions disclosed herein find utility. The ZFPs and nucleic acids can be used to treat significant wounds such as ulcers, pressure sores and venous ulcers and burns. Examples of such ulcers are those experienced by diabetic patients. An example of the use of ZFP fusions to promote wound healing is provided in Example 4 and FIG. 9.

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